

HOLLAND & KNIGHT LLP

One Atlantic Center
1201 West Peachtree Street, N.E.
Suite 2000
Atlanta, Georgia 30309-3400

404-817-8500
404-881-0470 Fax
www.hkllaw.com

Annapolis
Atlanta
Bethesda
Boston
Bradenton
Chicago*
Fort
Lauderdale
Jacksonville
Lakeland
Los Angeles
Miami
New York
Northern
Virginia
Orlando
Portland
Providence
St.
Petersburg
San Antonio

San Francisco
Seattle
Tallahassee
Tampa
Washington, D.C.
West Palm Beach

International
Offices:
Caracas**
Helsinki
Mexico City
Rio de Janeiro
São Paulo
Tel Aviv**
Tokyo

*Holland &
Knight LLC
**Representative
Office

RECEIVED
CENTRAL FAX CENTER

APR 05 2004

OFFICIAL

FACSIMILE**TO:**

U.S. Patent and
Trademark Office
COMPANY/FIRM

703-872-9306

NAME

FAX NUMBER

Alexandria

VA

703-308-1202

CITY

STATE

(TELEPHONE NUMBER)

FROM:

Patrea L. Pabst

404-817-8473

36

NAME

TELEPHONE

TOTAL PAGES (Including Cover Sheet)

FOR THE RECORD:

DATE: April 5, 2004

URGENCY: ☐ SUPER RUSH

☐ RUSH

☐ REGULAR

FAXED BY:

FILE #: 078617/00140

CLIENT NAME: OMRP 161 CIP

CONFIRMED: ☐ YES ☐ NO

NAME:

TIME:

If you did not receive all of
the pages or find that they
are illegible, please call
(404) 817-8500

CONFIDENTIALITY NOTICE: This facsimile, along with any documents, files,
or attachments, may contain information that is confidential, privileged, or
otherwise exempt from disclosure. If you are not the intended recipient or a
person responsible for delivering it to the intended recipient, you are hereby
notified that any disclosure, copying, printing, distribution or use of any
information contained in or attached to this facsimile is strictly prohibited. If
you have received this facsimile in error, please immediately notify us by
facsimile or by telephone collect at the numbers stated above, and destroy the
original facsimile and its attachments without reading, printing, or saving in any
manner. Your cooperation is appreciated. Thank you.

MESSAGE:

Appellants: John B. Harley, Judith A. James, and Kenneth M. Kaufman

Serial No: 09/500,904

Art Unit: 1648

Filed: February 9, 2000

Examiner: Foley, S.

For: DIAGNOSTICS AND THERAPY OF EPSTEIN-BARR VIRUS IN
AUTOIMMUNE DISORDERS

1439487.v1

PTO/SB/17 (10-03)

Approved for use through 07/31/2006. OMB 0651-0032
U.S. Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

FEE TRANSMITTAL
for FY 2004

Effective 10/01/2003. Patent fees are subject to annual revision.

☐ Applicant claims small entity status. See 37 CFR 1.27**TOTAL AMOUNT OF PAYMENT** (\$) -0-**Complete if Known**

Application Number	09/500,904
Filing Date	February 9, 2000
First Named Inventor	John B. Harley
Examiner Name	S. Foley
Art Unit	1648
Attorney Docket No.	QMRP 161 CIP

METHOD OF PAYMENT (check all that apply)☐ Check ☐ Credit card ☐ Money Order ☐ Other ☐ None☒ Deposit Account:Deposit
Account
Number
Deposit
Account
Name

50-1868

Holland & Knight LLP

The Director is authorized to: (check all that apply)

☒ Charge fee(s) indicated below ☒ Credit any overpayments☒ Charge any additional fee(s) or any underpayment of fee(s)☐ Charge fee(s) indicated below, except for the filing fee to the above-identified deposit account.**FEE CALCULATION****1. BASIC FILING FEE**

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description	Fee Paid
1001 770	2001 385	Utility filing fee	
1002 340	2002 170	Design filing fee	
1003 530	2003 265	Plant filing fee	
1004 770	2004 385	Reissue filing fee	
1005 160	2005 80	Provisional filing fee	
SUBTOTAL (1) (\$)			

2. EXTRA CLAIM FEES FOR UTILITY AND REISSUE

Total Claims	Extra Claims	Fee from below	Fee Paid
9	-20*	0	0
2	-3**	0	0
Multiple Dependent			

Large Entity Fee Code (\$)	Small Entity Fee Code (\$)	Fee Description	Fee Paid
1202 18	2202 9	Claims in excess of 20	
1201 86	2201 43	Independent claims in excess of 3	
1203 290	2203 145	Multiple dependent claim, if not paid	
1204 86	2204 43	** Reissue independent claims over original patent	
1205 18	2205 9	** Reissue claims in excess of 20 and over original patent	
SUBTOTAL (2) (\$)			-0-

*or number previously paid, if greater; For Reissues, see above

FEE CALCULATION (continued)**3. ADDITIONAL FEES**

Large Entity Small Entity

Fee Code (\$)	Fee Code (\$)	Fee Description	Fee Paid
1051 130	2051 65	Surcharge - late filing fee or oath	
1052 50	2052 25	Surcharge - late provisional filing fee or cover sheet	
1053 130	1053 130	Non-English specification	
1812 2,520	1812 2,520	For filing a request for <i>ex parte</i> reexamination	
1804 920*	1804 920*	Requesting publication of SIR prior to Examiner action	
1805 1,840*	1805 1,840*	Requesting publication of SIR after Examiner action	
1251 110	2251 55	Extension for reply within first month	
1252 420	2252 210	Extension for reply within second month	
1253 950	2253 475	Extension for reply within third month	
1254 1,480	2254 740	Extension for reply within fourth month	
1255 2,010	2255 1,005	Extension for reply within fifth month	
1401 330	2401 165	Notice of Appeal	
1402 330	2402 165	Filing a brief in support of an appeal	
1403 290	2403 145	Request for oral hearing	
1451 1,510	1451 1,510	Petition to institute a public use proceeding	
1452 110	2452 55	Petition to revive - unavoidable	
1453 1,330	2453 665	Petition to revive - unintentional	
1501 1,330	2501 665	Utility issue fee (or reissue)	
1502 450	2502 240	Design issue fee	
1503 640	2503 320	Plant issue fee	
1460 130	1480 130	Petitions to the Commissioner	
1807 50	1807 50	Processing fee under 37 CFR 1.17(q)	
1808 180	1808 180	Submission of Information Disclosure Stmt	
8021 40	8021 40	Recording each patent assignment per property (times number of properties)	
1809 770	2809 385	Filing a submission after final rejection (37 CFR 1.129(a))	
1810 770	2810 385	For each additional invention to be examined (37 CFR 1.129(b))	
1801 770	2801 385	Request for Continued Examination (RCE)	
1802 900	1802 900	Request for expedited examination of a design application	

Other fee (specify) Fee for Appeal Brief paid 1/6/03

*Reduced by Basic Filing Fee Paid

SUBTOTAL (3) (\$)**SUBMITTED BY**

Name (Print/Type)	Patrea L. Pabst	Registration No. (Attorney/Agent)	31,284	Telephone	(404) 817-8473
Signature		Date	April 5, 2004		

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

This collection of information is required by 37 CFR 1.17 and 1.27. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS.

SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

PTO/SB/21 (08-03)

Approved for use through 07/31/2006. OMB 0651-0031

U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FORM (to be used for all correspondence after initial filing)	Application Number	09/500,904
	Filing Date	February 9, 2000
	First Named Inventor	John B. Harley
	Art Unit	1648
	Examiner Name	S. Foley
Total Number of Pages in This Submission	Attorney Docket Number	OMRF 161 CIP

ENCLOSURES (Check all that apply)		
<input checked="" type="checkbox"/> Fee Transmittal Form <input type="checkbox"/> Fee Attached <input type="checkbox"/> Amendment/Reply <input type="checkbox"/> After Final <input type="checkbox"/> Affidavits/declaration(s) <input type="checkbox"/> Extension of Time Request <input type="checkbox"/> Express Abandonment Request <input type="checkbox"/> Information Disclosure Statement <input type="checkbox"/> Certified Copy of Priority Document(s) <input type="checkbox"/> Response to Missing Parts/Incomplete Application <input type="checkbox"/> Response to Missing Parts under 37 CFR 1.52 or 1.53	<input type="checkbox"/> Drawing(s) <input type="checkbox"/> Licensing-related Papers <input type="checkbox"/> Petition <input type="checkbox"/> Petition to Convert to a Provisional Application <input type="checkbox"/> Power of Attorney, Revocation <input type="checkbox"/> Change of Correspondence Address <input type="checkbox"/> Terminal Disclaimer <input type="checkbox"/> Request for Refund <input type="checkbox"/> CD, Number of CD(s) _____	<input type="checkbox"/> After Allowance communication to Group <input type="checkbox"/> Appeal Communication to Board of Appeals and Interferences <input checked="" type="checkbox"/> Appeal Communication to Group (Appeal Notice, Brief, Reply Brief) <input type="checkbox"/> Proprietary Information <input type="checkbox"/> Status Letter <input type="checkbox"/> Other Enclosure(s) (please identify below):
Remarks _____		
SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT		
Firm or Individual name	Patrea L. Pabst, Esq., Reg. No. 31,284 Holland & Knight LLP	
Signature	Suite 2000, One Atlantic Center, 1201 West Peachtree Street, N.E., Atlanta, GA 30309-3400	
Date	April 5, 2004	

CERTIFICATE OF TRANSMISSION/MAILING		
I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450 on the date shown below.		
Typed or printed name	Patrea L. Pabst	
Signature		Date April 5, 2004

This collection of information is required by 37 CFR 1.5. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants: John B. Harley, Judith A. James, and Kenneth M. Kaufman

Serial No: 09/500,904

Art Unit: 1648

Filed: February 9, 2000

Examiner: Foley, S.

For: **DIAGNOSTICS AND THERAPY OF EPSTEIN-BARR VIRUS IN
AUTOIMMUNE DISORDERS**

Commissioner for Patents
Washington, D. C. 20231

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 6-10 and 19-22 in the Office Action mailed November 5, 2003, in the above-identified patent application. A Notice of Appeal (and Replacement Supplemental Information Disclosure Statement) were filed on February 5, 2004. The fee for the filing of this Appellants' Brief was submitted with the previously filed Appeal Brief on January 6, 2003. The Examiner had withdrawn finality in view of this Appeal Brief, but reinstated the same rejections in the Office Actions mailed April 23, 2003 and November 5, 2003.

(1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignees, the Oklahoma Medical Research Foundation, Oklahoma City, OK, The Board of Regents of the University of Oklahoma Health Science Center, Oklahoma City, OK, and the licensee, JK Autoimmunity, Inc., Oklahoma City, OK.

U.S.S.N. 09/500,904
Filed: February 9, 2000
AMENDMENT

(2) RELATED APPEALS AND INTERFERENCES

The following related appeals are known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which may have a bearing on the Board's decision in this appeal:

U.S.S.N. 08/475,955 filed June 7, 1995. A copy of the decision in this application was placed in this file. The examiner questioned the relevance, but the undersigned believes that the technology is related and issues on appeal are related. U.S.S.N. 08/475,955 is drawn to the discovery of the viral peptides that elicit an autoimmune reaction in the patient, which are correlated with the development of lupus in patients previously exposed to the virus. The claims in this case are drawn to a diagnostic method which can use these peptides as antigen to measure levels of antibodies indicative of autoimmune disease in the patients exposed to the virus.

U.S.S.N. 08/781,296 filed January 13, 1997 by John B. Harley and Judith A. James entitled "Diagnostics and Therapy of Epstein-Barr Virus in Autoimmune Disorders", of which this is a continuation-in-part has been on appeal. The examiner changed and prosecution was reopened. It is possible the case will be back on appeal since the most recent office action reiterated the rejections on appeal.

(3) STATUS OF CLAIMS ON APPEAL

Claims 6-10 and 19-22 are pending and on appeal. The text of each claim on appeal, as amended, is set forth in the Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The pending claims were last amended by the Amendment mailed July 23, 2003.

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

(5) SUMMARY OF THE INVENTION

Differences have been identified in the immune responses to Epstein-Barr infection between individuals who develop a specific autoimmune disease and those who do not. (page 8, lines 20-22). These differences are used in the claimed diagnostic assay kits and methods of use thereof to distinguish those who are at greater risk for developing specific autoimmune diseases from those who are a lesser risk. (page 8, lines 22-24) Individuals who are not at as great a risk for developing autoimmune disease can be identified by reactivity to various peptides, for example, as demonstrated in the examples where individuals who are not prone to develop lupus are characterized by antibodies to GAGAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO: 7). (page 2, lines 15-19) Subsets of antigenic peptides can be used to identify patients at risk for particular clinical manifestations or patients in particular prognostic groups. (page 26, lines 21-23) The peptides can be used in combination in assays, such as the solid phase assay, to classify patients. (page 26, lines 23-24)

(6) ISSUES ON APPEAL

The issues presented on appeal are

- (1) whether claims 6-10 and 19-22 are enabled under 35 U.S.C. 112, first paragraph.
- (2) whether claims 6-10 and 19-22 are obvious under 35 U.S.C. 103 over Petersen, et al. Arthritis and Rheumatism 33(7):993-1000 (1990).
- (3) whether claims 6-10 and 19-22 are obvious under 35 U.S.C. 103 over Marchini, et al. J. Autoimmunity 7:179-191 (1994) in combination with Petersen, et al.

Claims 6-10 and 19-22 were *provisionally* rejected under the doctrine of obviousness-type double patenting over claim 35 of U.S.S.N. 08/781,296. This rejection will be addressed either by filing of an appropriate Terminal Disclaimer or by cancellation of claim 35 in the co-

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

pending application, once the claims have otherwise been determined to be allowable in the two applications.

(7) GROUPING OF CLAIMS

The claims do not stand or fall together, as discussed in more detail below.

(8) ARGUMENTS

(i) The Invention

Differences have been identified in the immune responses to Epstein-Barr infection between individuals who develop a specific autoimmune disease and those who do not. These differences are used to distinguish those who are at greater risk for developing specific autoimmune diseases from those who are a lesser risk. For example, individuals who are not at as great a risk for developing autoimmune disease can be identified by reactivity to the various peptides, for example, as demonstrated in the examples where individuals who are not prone to develop lupus are characterized by antibodies to GAGAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO: 7). Other structures derived from Epstein-Barr virus can be used to predict who will develop autoimmune disease. These structures were identified using standard techniques, the known sequences of the Epstein-Barr viral proteins and the known sequences of the autoantigens such as Srn B' and Ro/SSA, and sera from many patients, including a large data base that spanned a number of years in the same patients, allowing the appellants to follow the progression of the disease and markers for the disease, over a period of years. Comparison with normals or individuals who did not develop the disease allow those skilled in the art to identify individuals who are more likely than not to develop autoimmune disease.

The claims are drawn to the following:

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

Claim 6 has been amended to define a diagnostic assay or test for predicting the risk of developing lupus as including the following reagents:

(1) reagents which can be used to detect in a patient sample materials which are indicative of Epstein-Barr viral infection:

- (a) levels of antibodies to Epstein-Barr virus,
- (b) levels of indicators of Epstein-Barr infection of cells, or
- (c) levels of Epstein-Barr DNA or protein in a patient,

wherein the reagents used to detect antibodies to peptides from Epstein-Barr virus are peptides of up to forty amino acids in length comprising an amino acid sequence selected from the group consisting of PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3), GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGRGGGRPG (SEQ ID NO:98), GSGSGPRHRDGVRRPQKRP (SEQ ID NO:25), RPQKRPS (SEQ ID NO:26), QKRPSGCKGTHGGTG (SEQ ID NO:27), GTGAGAGARGRG (SEQ ID NO:99), SGGRGRGG (SEQ ID NO:100), RGGSGRRGRGR (SEQ ID NO:101), RARGRGRGRGEKRRS (SEQ ID NO:102), SSSGSPRRPPGR (SEQ ID NO:103), RPPGRJPFFHPVGEADYFEYHQEG (SEQ ID NO:104), PDVPPGAI (SEQ ID NO:33), PGAEQGA (SEQ ID NO:34), GPSTGPRG (SEQ ID NO:105), GQGDGGRK (SEQ ID NO:37), DGRRKKGGWFGKHR (SEQ ID NO:38), GKHRGQGSN (SEQ ID NO:106), GQGSNPK (SEQ ID NO:107), NPKFENIA (SEQ ID NO:108), RSHVERTT (SEQ ID NO:109), VFVYGGSKT (SEQ ID NO:110), GSKTSLYNL (SEQ ID NO:111), GMAPGPGP (SEQ ID NO:46), PQGPLRE (SEQ ID NO:47), CNIRVTV (SEQ ID NO:48), RVTVCFSDDG (SEQ ID NO:49), PPWFPPMVEG (SEQ ID NO:50) and the peptide consisting of GPQRRGGDNHGRGRGRGRGRGGGRPG (SEQ ID NO:98), and

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

(2) control samples from individuals not at risk of developing lupus, and
(3) means for determining the differences in the levels of a patient and control samples to distinguish individuals at higher risk of developing lupus from those at lower risk of developing lupus.

Claim 7 further defines the reagents of claim 6 for use in particular types of assays: assays based upon the relative presence of an antibody, assays based on cellular proliferation, assays based on molecular binding, assays based on cytokine production, assays based on skin reaction, and assays based on cell surface antigen.

Claim 8 limits the reagents to specific peptides used to detect antibodies, PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3), GAGAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGRGGGRPG (SEQ ID NO:98), GGSGSGPRHRDGVRRPQKRP (SEQ ID NO:25), RPQKRPS (SEQ ID NO:26), QKRPSIGCKGTHGGTG (SEQ ID NO:27), GTGAGAGARGRGG (SEQ ID NO:99), SGGRGRGG (SEQ ID NO:100), RGGSGRRGRGR (SEQ ID NO:101), RARGRGRGRGEKRPRS (SEQ ID NO:102), SSSSGSPRRPPPGR (SEQ ID NO:103), RPPPGRRPFFHPVGEADYFEYHQEG (SEQ ID NO:104), PDVPPGAI (SEQ ID NO:33), PGAIEQGPA (SEQ ID NO:34), GPSTGPRG (SEQ ID NO:105), GQGDGGRRK (SEQ ID NO:37), DGGRRKKGWFGKHR (SEQ ID NO:38), GKHRGQGGSN (SEQ ID NO:106), GQGGSNPK (SEQ ID NO:107), NPKFENIA (SEQ ID NO:108), RSHVERTT (SEQ ID NO:109), VFVYGGSKT (SEQ ID NO:110), GSKTSLYNL (SEQ ID NO:111), GMAPGPGP (SEQ ID NO:46), PQPGPLRE (SEQ ID NO:47), CNIRVTVC (SEQ ID NO:48), RVTVCSEDDG (SEQ ID NO:49), PPWFPPMVEG (SEQ ID NO:50).

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

Claim 9 limits the assay of claim 8 to a specific peptide which is predictive of an individual not developing lupus, GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7).

Claim 10 defines the assay as useful for testing patients identified with or at risk of developing systemic lupus erythematosus comprising control samples from individuals with systemic lupus erythematosus (in addition to controls who do not have lupus).

Claims 19-22 define methods paralleling the limitations of the diagnostic assay of claims 6-10.

Claim 19 defines a method for determining the likelihood that an individual has lupus induced by Epstein-Barr virus, or is at risk for developing lupus, including the steps of:

- (1) obtaining a sample from the individual to be tested,
- (2) mixing the sample with reagents which can be used to detect levels of
 - (a) antibodies to Epstein-Barr virus,
 - (b) indicators of Epstein-Barr infection of cells, or
 - (c) levels of Epstein-Barr DNA or protein in a patient,
- (3) analyzing the sample, and
- (4) comparing the analysis of the sample with results obtained with control samples from individuals not at risk of developing lupus to determine if the differences in levels of the individual and control samples indicates the individual is at a higher risk of developing lupus than controls who are at lower risk of developing lupus.

Claim 20 parallels claim 7. Claims 21 and 22 define the same peptides as claims 8 and 9.

The methods defined by these claims are fully supported by several actual working examples in the specification, showing that the claimed method is predictive of the likelihood one will or will not develop an autoimmune disease such as lupus.

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

Example 1 is a study to determine which of 233 overlapping octapeptides in an autoantigen, Sm B', are indicative of disease. As shown by Figure 2, all of the anti-Sm sera (i.e., from patients with lupus) tested bound almost the identical octapeptide structures. As demonstrated by the data in the example, anti-Sm sera binds to PPPGMRPP and structurally similar sequences (Figure 3 SEQ ID NO:4). These sequences included PPPGRRP (SEQ ID NO:1), which is found in the Epstein-Barr Nuclear Antigen-1 (EBNA-1) protein. GRGRGRGG (SEQ ID NO:2) and RGRGREK (SEQ ID NO:3) are also sequences from Epstein-Barr virus Nuclear Antigen-1, but these are similar to a major antigenic epitope of Sm D in lupus patients, GRGRGRGRGRGRGRGRGRGRGGPRRR (SEQ ID NO:9). All three peptides bind at least three times more antibody from the anti-Sm precipitin positive lupus patient sera than the controls. The antibody binding to these peptides in the lupus patient sera was over half of the antibody binding level found for PPPGMRPP (SEQ ID NO:4).

Data was also obtained using a collection of about 80,000 specimens from 26,000 individuals collected and stored over a period of 17 years. This Clinical Immunology database was screened to identify lupus patients who developed anti-Sm under observation. The clinical serum bank was found to contain stored serum specimens from 161 patients with anti-Sm antibodies in at least one serum sample. Four patients were identified among these who, during their SLE clinical course or after initial presentation, converted from being precipitin negative to precipitin positive for antibodies to Sm. Sera from each individual were retrieved from before and after the development of anti-Sm antibodies. For each serum sample, antibody levels were tested by ELISA for binding to Sm and the Sm/nRNP complex. The Ro protein was selected as a control antigen since none of the four patients demonstrated anti-Ro antibodies by Ouchterlony immunodiffusion. Each patient increased binding towards the Sm and Sm/nRNP antigens over

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

time, without an increase in binding to the Ro protein (above background levels) by ELISA. Anti Sm B/B' indicated specificity was confirmed by Western blotting. Binding to Sm B/B' indicated acquisition of a new antibody specificity, since binding to this protein was not detected in the first available sample tested from each patient. Each available serum sample was tested for antibody binding to the 233 overlapping octapeptides of Sm B/B'. Each patient had antibodies which initially targeted the proline rich, repeated motif, PPPGMRP(G)P (SEQ ID NO:4). With time the response diversified to other regions of Sm B/B' when additional serum samples were available.

Sm positive patients from whom a serum sample was available from presentation were also screened. Serum samples from lupus patients stored early in the course of the disease process bind only PPPGMRPP (SEQ ID NO:4) (and neighboring peptides) of the 233 possible octapeptides of B/B', as shown by Figure 4 for one such patient. In addition to the patient presented in Figure 4, two others who initially had a simplified pattern of octapeptide binding were identified. In all three of these cases, only PPPGMRPP (SEQ ID NO:4) and PPPGMRGP (SEQ ID NO:8) were bound and no other octapeptide were bound. All other anti-Sm positive sera tested bind these octapeptides as well as others. These results are consistent with PPPGMRPP (SEQ ID NO:4) and PPPGMRGP (SEQ ID NO:8) being the first epitopes of the Sm B/B' autoantigen (Arbuckle, M. R., et al., Scan. J. Immunol. 50:447-55, 1999). This repeated PPPGMRPP (SEQ ID NO:4) motif is an early target in three additional patients tested from whom sera were available from early in their disease. In all of these patients PPPGMRPP (SEQ ID NO:4) is the first autoimmune epitope of the Sm B/B' autoantigen against which one can detect antibody binding.

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

Four peptide sequences from Epstein-Barr virus were separately evaluated for binding to sera from patients with an autoimmune disease (Figures 3 and 7). All are found in the EBNA-1 (Epstein-Barr virus Nuclear Antigen-1) protein. Subjects with an autoimmune disease, systemic lupus erythematosus, have higher levels of antibodies against PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2) and RGRGREK (SEQ ID NO:3) than do normal controls. On the other hand the glycine-alanine repeat sequence, GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), which, after infection by Epstein-Barr virus, is a major epitope in infectious mononucleosis and in normals (Rhodes, G. et al. *J. Exp. Med.* 165:1026-1040 (1987)) tends not to be bound by patients with lupus (Figure 7). Figure 7 is a graph of the binding to the peptide GAGAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7) from Epstein-Barr virus Nuclear Antigen-1 by lupus sera who all had anti-Sm and anti-nRNP precipitins, as compared to normal control sera. The structures (octapeptides from Epstein-Bar virus nuclear antigen-1) bound by the lupus sera tested is listed in Table 8. These are taken from epitopes with average binding greater than 3 standard deviations about the normal mean (of EBV positive normal controls) and commonly bound by patient sera with an O.D. greater than 0.45 absorbance units. Sequences longer than eight amino acids represent neighboring octapeptides that exceed the 0.450 A U.

Other sequences have also been identified. As described by Example 10, PPPGMRPP (SEQ ID NO:4) constructed on a multiple antigenic peptide (MAP) backbone was coupled to CNBr activated Sepharose™. Each MAP molecule contains eight copies of the PPPGMRPP (SEQ ID NO:4) peptide on a branching polylysine backbone. One ml of sera from a Sm precipitin positive black female lupus patient was passed over the column and extensively washed. Bound antibodies were removed with 3 M guanidine and then dialyzed against 25 mM Tris-HCl pH 8.0. The column affinity purification was repeated using the first round bound

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

material. Purified antibodies were concentrated and quantitated by UV absorption. In order to identify the peptide epitopes recognized by human anti-PPPGMRPP (SEQ ID NO:4) antibodies, a random heptapeptide phage display library from New England Biolabs (Bar Harbor, MA) was screened. A heptapeptide library was selected because all 1.28×10^9 seven amino acid possibilities could be represented (8 a.a. = 2.56×10^{10} combinations, 9 a.a. = 5.12×10^{11} combinations). In this library each random heptapeptide is expressed at the N-terminus of the pIII minor phage coat protein followed by a Gly-Gly-Gly spacer. There is on average five copies of the pIII protein per phage particle. Theoretically, every combination of seven amino acid sequences could be expressed. Antibody-phage complexes were isolated by incubation with protein-A agarose. Following the fourth round of amplification, 70 clones were isolated and sequenced (Table 9). Eleven distinct sequence motifs were identified. Both class I and class II motifs share obvious homology to PPPGMRPP (SEQ ID NO:4) peptide. The binding of anti-PPPGMRPP (SEQ ID NO:4) antibodies to the different types of peptides displayed on the phage was then characterized. Figures 8A-E are graphs of the binding to the overlapping octapeptides from Epstein-Barr virus Nuclear Antigen-1. The binding of three controls are presented in Figures 8A, 8B and 8C and that of two lupus sera in Figures 8D and 8E. Figure 8A is from a normal who has no evidence of having been infected by Epstein-Barr virus by the assay for anti-Epstein-Barr virus Viral Capsid Antigen IgG. The other sera presented (Figures 8B through 8E) are all positive in this assay. The peptides presented had average reactivity at least 3 standard deviations above the normal mean. Sequences longer than eight amino acids represent neighboring octapeptides that exceed the 0.450 A.U. threshold.

Example 9 demonstrates that one can screen for the antibodies using cell line lysates rather than the peptides. Three different cell lines: B95 (marmoset cell line with the most

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

common strain, EBV-1 or --A), Jiyoye cell line (from Burkitt's lymphoma with EBV-2 or --B), and the Ramos cell line which has no EBV infection were obtained. 15 patient and 13 control sera were screened for binding to these different cells lysates. Anti-EBNA-1 is quite obvious as an approximate 70 kD band. All 15 patient sera, as well as 11 of 13 control sera, strongly bind the EBNA-1 protein in both strains. An EBNA-1 monoclonal antibody confirms the identify of this band. Many other proteins are bound by patient and control sera, however there appears to be more patient sera binding to approximately 90 kD, 58 kD, 50 kD, and 36 kD bands.

In summary, the claims define a diagnostic kit and method of use for determining the likelihood that an individual will develop an autoimmune disease. As the examples demonstrate, these assays, and reagents for use therein, have been made, tested, and demonstrated to yield statistically significant results. The examples clearly *establish a statistically significant correlation between EBV and lupus. There is no other legal requirement.*

(ii) Rejection Under 35 U.S.C. § 112, enablement

(a) The legal requirements under 35 U.S.C. 101 and 112, first paragraph

An invention must have utility. This requirement can be found in U.S.C. § 101 which states, "Whoever invents or discovers any new and *useful* process or . . . composition of matter . . . may obtain a patent . . ." (emphasis added). This requirement is also implicitly found in 35 U.S.C. § 112 which requires the specification to provide a written description for "making and *using*" the claimed subject matter.

Whether the utility requirement comes from 35 U.S.C. § 101 or 35 U.S.C. § 112, the standard to be applied is the same. *Ex parte Maus*, 14 USPQ2d 1762, 9 USPQ2d 1746, 1747 (Bd. Pat. App. & Int'l 1987). The *Maus* court stated, "the issue under 35 U.S.C. § 112 relating to an enabling disclosure is subsumed within the issue under 35 U.S.C. § 101 relating to patentable

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

utility." Any analysis of a claim under 35 U.S.C. § 112, first paragraph relating to the use of the claimed subject matter, need only meet the standards of the utility requirement of 35 U.S.C. § 101 because if the claimed subject matter meets the utility requirement it is presumed to meet the enablement requirement of use.

To meet the utility requirement the invention must simply have a "practical utility" in the "real world sense." (*Nelson v. Bowler*, 626 F.2d 853, 856 (CCPA, 1980)). Any use which gives immediate benefit to the public is sufficient to be a "practical utility". *Id.* at 856. It is clear that for an invention to have "practical utility" it must be operative. However, to fail the utility requirement the claimed subject matter must be "totally incapable of achieving a useful result. ("In short, the defense of non-utility cannot be sustained without proof of total incapacity.")") (*Brooktree Corp v. Advanced Micro Devices, Inc.*, 977 F.2d 1555 (Fed. Cir. 1992). See also *E.I. du Pont De Nemours and Co. v. Berkley and Co.*, 620 F.2d 1247, 1260 n.17, 205 USPQ 1, 10 n.17 (8th Cir. 1980). An assertion of utility is sufficient to meet the utility requirement unless the assertion is "incredible in the light of the art or factually misleading." (*In re Citron*, 325 F.2d 1389 (CCPA, 1963)).

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (See, e.g., *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Teletronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

affirmed by the Court in Spectra-Physics, Inc. v. Coherent, Inc., 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether making or using the invention would have required undue experimentation, and thus whether the disclosure is enabling, is a legal conclusion based upon several underlying factual inquiries. See In re Wands, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in Wands, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' Atlas Powder Co., v. E.I. DuPont De Nemours & Co., 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

The test is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Ex parte Jackson, 217 USPQ 804, 807 (1982)

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

As stated in the MANUAL OF PATENT EXAMINING PROCEDURE §2164.04 (7th ed. 1998), citing In re Wright, 999 F.2d 1557, 1562 (Fed. Cir. 1993), the examiner has the initial burden to establish a reasonable basis to question the enablement of the application.

A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken as being in compliance with the enablement requirement** of 35 U.S.C. § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Id. at § 2164.05 (emphasis added).

(b) *The claims comply with 35 U.S.C. 112, first paragraph*

The Examiner's argument in support of the rejection begins with an incorrect premise: "the specification, while being enabling for detecting the presence of EBV, does not reasonably provide enablement for predicting the risk of developing lupus by detecting the presence of EBV." (last line page 3 - top of page 4, office action mailed November 5, 2003).

Appellants are not detecting the presence of EBV.

Appellants are detecting the presence of antibodies to very specific antigens found within certain EBV proteins.

The data in the application show that individuals who have never been infected with EBV do not have antibodies to any of the EBV antigens - neither those that are predictive of developing lupus nor those that are predictive of not developing lupus. This is what one skilled in the art would expect.

U.S.S.N.: 09/500,904
Filed: February 9, 2009
AMENDMENT

However, the data in the application also demonstrates that *following infection, indeed, long after the viral infection has disappeared*, individuals develop antibodies to different viral epitopes. It is the specificity of these antibodies that determines the likelihood the individual will develop lupus, and indicate if the individual has already developed lupus.

In a totally unexpected finding, possible because appellants had access to thousands of samples collected over decades, including samples collected over extensive periods of time for the *same individuals*, appellants demonstrated that antibodies that arose due to the initial viral infection expand in their specificity to encompass epitopes that were not reactive with the initial antibodies. When these epitopes are also present in "self" proteins, the antibodies elicited by the original viral infection become "autoantibodies", i.e., antibodies against "self", causing lupus, a devastating autoimmune disease.

The examiner's arguments on page 5 of the office action rely on the fact that the prior art does not disclose that which is claimed! Of course the prior art does not disclose what is claimed: the prior art did not have access to the samples that appellants were able to test and analyze, nor did the prior art recognize "epitope spreading", a phenomena only very recently understood, primarily based on appellants' work.

There is no legal requirement that the prior art support the claimed method - indeed, what makes the claimed method and reagents patentable is that they are neither disclosed by, nor obvious from, the prior art, as discussed in more detail below.

The examiner's position is similar to that encountered by the researcher who discovered that many stomach ulcers are caused by a little known bacteria called *Helicobacter pylori* - all the prior art said stomach ulcers were caused by stress, not bacteria. Now the first line of

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

treatment for stomach ulcers is antibiotics. Just because the prior art does not support the appellants' position does not mean it lacks enablement.

The examiner's focus on the alleged lack of appropriate controls is simply wrong. Appellants state that one can use as controls individuals who do not develop lupus. Although these are individuals who do not have antibodies with the claimed reactivity, they are also readily identified by those skilled in the art as not having the characteristics defined by the American College of Rheumatologists for lupus patients.

Appellants have met the legal requirements. As discussed above, the application contains a number of examples that show that one can differentiate between samples of patients with lupus and controls that do not have lupus, both prior to development of symptoms as well as after development of symptoms. These examples demonstrate that specific peptide sequences have been obtained which can be used to screen sera from patients for antibodies which bind to the peptides, some of which are indicative of disease (to a degree that there is 300% more binding from those with or developing disease as compared to negative controls) and some of which are indicative that a patient will not develop disease (the peptide of claims 9 and 22). The examples also demonstrate that assays using cell lysates in functional assays (as defined by claims 7 and 20) can show differences between the two groups, as well as assays for Epstein-Barr DNA. These examples are not hypothetical. They are based on actual patient samples. There are two groups of patients - those being tested after they have developed the symptoms of the disease and those for whom samples are available both before and after development of symptoms. The assay has been shown to be predictive with these samples as well - demonstrating that appellants had in their possession no later than the date of filing of this application, the claimed diagnostic assay and method of use thereof, that they had described the assay and method of use thereof in

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

sufficient detail to enable anyone of skill in the art to make and use the claimed assay and method, and that the method had utility.

The test for enablement, whether one skilled in the art could practice the claimed method, and make and use the claimed reagents, without undue experimentation, based on the specification, has clearly been met.

The test contains reagents such as antibodies to EBV antibodies, EBV proteins, or proteins which are known indicators of EBV infection; control samples which are used to eliminate "background" reactions with the reagents not indicative of developing lupus; and means for distinguishing the background reactions (i.e., the reactions between the reagents and the control samples) and the patient samples. If the reaction is greater with the patient sample than with the controls, the patient is at risk. The means are standard - in some cases, the means may be an ELISA assay, where a colored reaction is titrated to quantitate the number of reactants; it may be a chromatographic assay where a spectrophotometer is used to measure the intensity of the reaction; it may be an immunoprecipitation assay. This is certainly a relative analysis, but one commonly practiced by those skilled in the art. Who has not had a blood analysis in which each determination is followed by the normal range, so that one can determine whether one is within the normal range or outside the normal range, and therefore at a great risk?

Claims 6-10 and 19-22 use the terms "likelihood" and "at risk". The terms are well known to those skilled in the art. Particularly in a case such as lupus, where there is a genetic component (same as in some types of cancer or heart disease), there are tests that can be performed to indicate if an individual is more likely than the average individual to develop a disorder, in this case, lupus. There is no legal requirement that one must establish a cause-and-effect between EBV and lupus before one can claim an assay, this is not the legal standard. The

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

requirement for enablement is whether or not one can make and use that which is claimed. The only essential outcome is whether or not the patient has, or is more likely than not to, develop lupus - which is all many physicians require before initiating far more expensive and comprehensive testing which would be more definitive.

In addition to the evidence in the specification, three abstracts have been submitted which provide evidence that EBV infection is at a minimum correlated with lupus:

Verdolini, et al., Br. J. Dermatol. 146(5):877-881(2002)

Dror, et al. Am. J. Kidney Dis. 32(5):825-828 (1998)

James, et al., Arthritis Rheum. 44(5):1122-1126 (2001)

No more is required under 35 U.S.C. 112, first paragraph. There is no legal requirement to "conclusively" correlate evidence that EBV cause autoimmune disease - the claims are drawn only to an assay and method of predicting the likelihood that a patient will develop the disease. This appellants have shown, using samples obtained from patients and negative controls prior to and after development of disease. Moreover, appellants have described these assays in sufficient detail to enable one skilled in the art, without undue experimentation, to practice the same assays, using the same reagents as claimed. The examiner has provided no evidence to the contrary. All that has been cited in support of the rejection is that the prior art does not establish that the claimed assay and method is useful. This, of course, is not the test under 35 U.S.C. 112.

In summary, claims 6-10 and 19-22 meet the requirements under 35 U.S.C. 112, first paragraph.

(iii) Rejections under 35 U.S.C. 103

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

Claims 6-10 and 19-22 were rejected under 35 U.S.C. 103 as obvious over Petersen, et al., , Arthritis and Rheumatism 33(7):993-1000 (1990) or the combination of Marchini, et al. J. Autoimmunity 7:179-191 (1994) and Petersen, et al.

a. *Marchini, et al.*

Marchini, et al. does not teach that one can predict the likelihood of developing lupus based on an EBV infection. As the examiner has correctly noted, Marchini looks at antibodies in lupus patients and determines whether or not they are reactive with EBV and Smd, an autoantigen.

b. *Petersen, et al.*

Petersen also does not teach that EBV viral infection is predictive of the likelihood of developing lupus. Petersen, et al. only looks at samples *after infection and development of autoimmune disease*, same as Marchini. As the examiner correctly notes, Petersen does not teach the claimed peptides, *much less that some are used to indicate the likelihood some will develop lupus and some will not*. Only with experimental data and extensive statistical analysis can one determine that there is a correlation between EBV infection and whether someone develops lupus. The examiner has recognized this as well.

With respect to the sequences that the examiner has cited, which is relevant only to the assay claims, these are different from the claimed sequences. The examiner, on page 9 of the office action, states that Petersen, et al., teaches the amino acid sequence of EBNA-1. However, appellants are not claiming the amino acid sequence of EBNA-1. To the extent that appellants are claiming peptides, these are very specific sequences within the protein. The claimed peptides are limited to the specified sequences, or peptides of no more than forty amino acids containing

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

these sequences. The examiner has pointed out where there is overlap, and where certain sequences fall within a much longer peptide. This is not enough.

To make the claimed peptides obvious, the prior art must disclose the specific sequence and a teaching that would lead one to select the claimed sequence. To make obvious a diagnostic kit, or method of use thereof, the prior art must go further, and teach one that the peptide would be useful in determining whether or not an individual would be predictive of a patient having or developing lupus.

None of the prior art does this. There is absolutely nothing in Marchini or Petersen that leads one to the claimed peptides, nor to have a reasonable expectation of success. "the clear difference in epitope specificity in each group of patients", where the difference in the groups is rheumatoid arthritis and convalescent mononucleosis patients, does not lead to who is expected to develop autoimmune disease - the second group may in fact ultimately overlap with the first group! The invention is to understand that one can correlate the likelihood of disease, or development of disease, with reactivity with *specific peptides*, not just any EBV peptides.

Therefore, the prior art fails to teach the claimed elements, how to modify the sequences to arrive at those claimed by applicants, or any reasonable expectation of success.

Indeed, Petersen, et al. teaches away from the claimed method because Petersen only looks at patients *after* they have developed the autoimmune disease; applicants claims require testing *prior to development of the autoimmune disease* - indeed, what would the point be *after the disease has occurred* - one clearly knows at that point that the patient is going to develop autoimmune disease.

There is nothing to lead one of ordinary skill in the art to the claimed peptides. It is not enough to say someone would have motivation to look for a reagent: the prior art must lead one

U.S.S.N.: 09/500,904
Filed: February 9, 2000
AMENDMENT

skilled in the art to what is claimed, with a reasonable expectation of success. Therefore the claimed reagents cannot be obvious over Petersen.

(9) SUMMARY AND CONCLUSION

Based on the foregoing, the compositions of claims 6-10 and methods of claims 19-22 are enabled and not obvious over the prior art.

Respectfully submitted,



Patrea I. Pabst
Reg. No. 31,284

Date: April 5, 2004
HOLLAND & KNIGHT LLP
2000 One Atlantic Center
1201 West Peachtree Street
Atlanta, Georgia 30309-3400
404-817-8473
404-817-8588 (Fax)